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# **Remission and recovery from first-episode psychosis in adults: A systematic review and meta-analysis of long term outcome studies**

Running title: remission and recovery in FEP

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### **Declaration of interest**

Two authors (FG and RMM) have a declaration of interest but not in relation to this work. FG has received honoraria for advisory work and lectures from Roche, BMS, Lundbeck, Otsuka and Sunovion, is a collaborator on a NHS Innovations project co-funded by Janssen and has a family member with professional links to Lilly and GSK, including stock.

RMM has received payment for lectures including service on speakers' bureaus for BMS, Janssen, AZ.

The other authors, JL, OA, BS, MC and KCM have no conflict of interest to declare.

### **Ethics statement:**

Ethical approval was not needed as this is a manuscript reports a systematic review or meta-analysis of observational studies

## **Abstract**

### **Background**

Remission and recovery rates for people with a First Episode Psychosis (FEP) remain uncertain.

### **Aims**

We conducted a systematic review and meta-analysis to assess pooled prevalence rates of remission and recovery in FEP in longitudinal studies and conducted meta regression analyses to investigate potential moderators.

### **Method**

Longitudinal studies with follow up greater than 1 year reporting data on remission or recovery rates in FEP were included.

### **Results**

Seventy nine studies were included representing 19,072 FEP patients(mean age=26.9years,male=59.5%).The pooled rate of remission among 12,301 individuals with FEP was 57.9%(95%CI=52.7-62.9,n=60 studies,mean follow-up=5.5 years). Higher remission rates were moderated by studies from more recent years. The pooled prevalence of recovery among 9,642 individuals with FEP was 37.9%(95%CI=30.0-46.5,n=35,mean follow-up=7.2 years). Recovery rates were higher in North America compared to other regions.

### **Conclusions**

Our data suggest that remission and recovery rates in FEP may be more favourable than previously thought. We observed stability of recovery rates after the first two years, suggesting that a progressive deteriorating course of illness is not typical.

While remission rates have improved over time, recovery rates have not, raising questions about the effectiveness of services in achieving improved recovery.

**Key words:**

First episode psychosis; schizophrenia; remission; recovery; outcomes; meta-analysis

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## Introduction

Psychotic disorders are marked by heterogeneity in terms of clinical presentation and outcome.<sup>1</sup> Historically, schizophrenia was conceptualised as a chronic, progressive deteriorating condition. However, there is increasing recognition that people with schizophrenia can experience symptomatic improvements and regain a degree of social and occupational functioning.<sup>2</sup> Over the past 20 years there has been an increased focus on specialist early intervention services for first episode psychosis (FEP).<sup>3, 4</sup> However, it remains unclear what the outcomes are for people with FEP (including those with first episode schizophrenia (FES) in terms of remission and recovery.

To our knowledge, only 3 systematic reviews and 2 meta-analyses have considered recovery or remission in FEP and/or schizophrenia.<sup>5-9</sup> The most recent systematic review and meta-analysis concluded that only 13.5% of schizophrenia patients met the criteria for recovery, though the follow up period is not given, and this review included both FES and multi episode schizophrenia patients.<sup>9</sup> Multi episode patients include those with more chronic or treatment resistant illnesses, who would by definition be expected to have lower recovery rates.

A systematic review in FEP identified 'good' outcomes for 42% of patients with psychosis and 31% of schizophrenia patients,<sup>7</sup> while a later review of remission in FEP identified an average remission rate of 40% (range 17%-78%).<sup>6</sup> These reviews in FEP have been limited by wide variety of outcome definitions used,<sup>7</sup> in keeping with a paucity of identified studies using standardized definitions of remission or recovery, a small number of included studies,<sup>6</sup> and no FEP review including a meta-analysis.

While naturalistic FEP outcome studies of increasing sophistication and duration have been published,<sup>10-13</sup> the longer term outcomes for these patients in terms of remission and recovery rates remains uncertain. This deficiency in the literature is important, as, since the introduction of the Remission in Schizophrenia Working

Group (RSWG) criteria for remission in 2005, many studies in FEP have sought to use the operationalized criteria for remission in schizophrenia.<sup>14</sup>

We, therefore, conducted a systematic review and meta-analysis to assess pooled prevalence rates of remission and recovery in FEP and FES in longitudinal studies. In addition, we sought to identify potential moderators of remission and recovery. Finally, we sought to investigate if specific variables have an impact on remission and recovery proportions (e.g. narrow and broad remission and recovery definitions, duration of follow-up, region of study and the study year).

Our a priori hypotheses were the following:

1. A greater proportion of patients with FEP will meet criteria for remission and recovery in studies from the past twenty years compared to earlier studies.
2. Recovery will be less prevalent in samples with longer duration of follow-up compared with shorter follow-up.
3. Rates of remission and recovery will be lower with the use of narrow criteria for defining remission and recovery.

## Methods

This systematic review was conducted in accord with the Meta-analysis of Observational Studies in Epidemiology guidelines<sup>15</sup> and the Preferred Reporting Items for Systematic Reviews and Meta-analyses standard.<sup>16</sup>

### Inclusion criteria

We included studies of longitudinal observational design (both retrospective and prospective studies) in patients >16 years old (with no upper age limit) that fulfilled the following criteria:

A) i) reporting remission rates and/or ii) recovery rates in people with a FEP (including FES and first episode affective psychosis) irrespective of clinical setting (inpatient, outpatient or mixed).

Remission has been operationalized in terms of symptomatic and/or functional improvement with a duration component. The use of the Remission in Schizophrenia Working Group (RSWG) criteria has become common over the past decade measuring both an improvement in symptoms and duration criteria (>6 months) for persistence of mild or absent symptoms.<sup>14</sup>

For remission, we categorised remission criteria into broad and narrow criteria for defining remission. Those studies in which remission was defined by the RSWG criteria (composed of two dimensions, accounting for symptom severity (mild or absent) and a duration criterion of mild or absent symptoms of  $\geq 6$  months) or if defined as patients being asymptomatic & attaining pre-morbid functioning sustained for  $\geq 6$  months, were classified as narrow criteria for remission. Those studies which defined symptomatic remission, but not a duration were classified as broad criteria.

Recovery has been operationalised as a multidimensional concept, incorporating symptomatic, and functional improvement in social, occupational and educational domains, with a necessary duration component (>2 years).<sup>9, 17, 18</sup> For recovery, we mirrored the approach of Jääskeläinen et al., 2013, categorising those studies in



which both clinical and functioning dimensions are operationally assessed, along with a duration of sustained improvement for  $\geq 2$  years.<sup>9</sup> We further analysed recovery in relation to those studies in which both clinical and level of functioning dimensions were assessed, but with a duration for sustained improvement of  $>1$  year. We categorised as broad recovery criteria those studies in which either one or none of the symptom improvement and functioning dimensions were used and/or with an insufficient duration criterion

B) People with FEP who were making their first treatment contact (in both inpatient and outpatient settings)

C) Using a specified standardized diagnostic system (e.g. ICD (International Classification of Diseases, versions 8,9 and 10), DSM (Diagnostic and Statistical Manual of Mental Disorders (DSM versions III and IV), Kraepelin & Feighner's diagnostic criteria, Royal Park Multidiagnostic Instrument for Psychosis, and the Research Diagnostic Criteria (RDC)

D) Study sample that included 100% individuals with FEP, and/or FES and/or first episode affective psychosis. When more than one diagnostic group was identified in a sample, that study was only included if the number in each subgroup was identified

E) A follow up period of  $> 12$  months

F) Studies with adequate follow up data to allow for remission or recovery rates to be determined (e.g. studies only reporting mean difference in symptom rating scales between groups or correlations were excluded)

G) Articles published in a peer reviewed journal from database inception to July 2016, with no language restrictions applied

### **Exclusion criteria**

Exclusion criteria were:

A) Randomized controlled trials (RCTs) due to the potential for any structured

intervention beyond routine care to influence our primary outcomes

B) Studies of organic psychosis.

### **Search criteria**

Two independent authors (JL, OA) searched PubMed, Medline, and Scopus without language restrictions from database inception until July 1, 2016. Key words used were “first episode psychosis” OR “early episode psychosis” OR “schizophrenia” OR “schiz\*” AND “remission” OR “recovery” AND “outcome” OR “follow-up”. Manual searches were also conducted using the reference lists from recovered articles and recent reviews.<sup>6, 7, 9</sup>

### **Data Extraction**

Two authors (JL and OA) extracted all data, and any inconsistencies were resolved by consensus or by a third author (BS). One author (OA) extracted data using a predetermined data extraction form, which was subsequently validated by a second author (JL). The data extracted included first author, country, setting, population, study design (e.g. prospective, retrospective), participants included in the study (including mean age, % female), diagnostic classification method, method of assessment (e.g. face-face interviews, case records, or combination of both approaches), duration of untreated psychosis (DUP), socio-demographic characteristics of the sample employed in the study (e.g., % employed, single or in stable relationship at the study entry), baseline psychotic symptoms (mean scores), length of study follow up, participant loss at follow up, and criteria used to define remission and recovery. When studies reported on overlapping samples, details of the study with the longest follow up were included, or if this was unclear, studies with the largest study sample for each respective outcome were included. We included multi-site studies, and retained data for the entire cohort and not for individual sites.

## **Primary outcomes**

The co-primary outcomes were the proportion of people with FEP who met the criteria for a) remission and b) recovery over the course of each study as defined above.

## **Statistical analysis**

Due to the anticipated heterogeneity across studies, we conducted a random effects meta-analysis. The meta-analysis was conducted in the following sequence. First, we calculated the pooled prevalence rates of remission and recovery in FEP. Second, in order to account for attrition bias, we imputed a remission and recovery rate using the principle of worst case scenario assuming all people who dropped out did not have a favourable outcome. Third, we calculated the subgroup differences in remission and recovery according to whether a narrow or broad definition of remission or recovery was used, the first episode diagnosis category, the method used to assess remission and recovery (structured face-to-face assessment; structured assessment supplemented with clinical notes and/or interviews with parents; clinical records), duration of follow-up (categorised into three groups: 1-2 years; 2-6 years; >6 years based on ascending duration of follow-up (tertiles)), region of study, the study period (we selected the midpoint of the study period as the study year, and categorized this by adapting criteria proposed by Warner et al. <sup>5</sup> for recovery studies-pre 1975; 1976-1996; 1997-2016; and for remission studies-pre 1975; 1976-1996; 1997-2004; 2005-2016), the study design, and the setting of the study at FEP (inpatient; community & early intervention services; and mixed in-and out-patient psychiatric services).

Fourth, we conducted meta-regression analyses to investigate potential moderators of remission and recovery (age, percentage of males, ethnicity, baseline psychotic symptoms (mean scores), relationship and employment status at first contact, DUP,

duration of follow up, attrition rate and study year.

Publication bias was assessed with the funnel plot, Egger regression test,<sup>19</sup> and the “trim and fill” method.<sup>20</sup>

Heterogeneity was measured with the Q statistic, yielding a chi-square and p-value, and the I<sup>2</sup> statistic with scores above 50% and 75% indicating moderate and high heterogeneity.<sup>21</sup>

Finally, descriptive statistical methods were used for the exploratory summary of study- reported correlates of remission and recovery based on patient-level data not available for study-level meta-regression analyses.

All analysis was conducted with Comprehensive Meta-Analysis software (CMA, Version 3) and STATA release 14 (STATACorp LP, USA).

## **Results**

### ***Search results and included participants***

Our search yielded 3021 non-duplicated publications, which were considered at the title, and abstract level; 299 full texts were reviewed, of which 79 met inclusion criteria (Figure 1).<sup>10-13, 22-96</sup> Full details of the included studies are included in supplementary table 1 (studies with remission as outcome) and supplementary table 2(studies with recovery as outcome). There were 44 studies reporting on remission rates and 19 reporting on recovery rates, with 16 studies reporting on both remission and recovery, for an overall of 79 independent samples. The final sample comprised 19,072 FEP patients (range of sample sizes: 13-2,842), with 12,301 (range sample sizes 13-2,210) with remission data and 9,642 (range of sample sizes 25-2,842) with recovery data.

*Remission sample:* The mean age of the patients at study recruitment was 26.3 years (median 25.7 years, age range 15.6-42.3) and 40.6% were females. The mean

DUP (N=25 studies) was 433.2 days (SD=238.9, IQR=265.0-541.4). The mean follow-up period was 5.5 years (N=60, 66.0 months, SD=5.3, IQR=2.0-7.0).

*Recovery sample:* The mean age of the patients at study recruitment was 27.3 years (median 26.0 years, range 24.2-28.5) and 41.1% were female. The mean DUP (N=11 studies) was 359.2 days (SD=215.4, IQR=226.3-492.8). The mean follow-up period was 7.2 years (N=35, 86.4 months, SD=5.6, IQR=2.0-10.0).

### **Meta-analysis of remission and recovery:**

#### ***Rate of remission***

The pooled rate of remission among 19,072 individuals with FEP was 57.9% (95% CI=52.7-62.9, Q=1536.3,  $p<0.001$ , N=60)(see Figure S1 in the online data supplement). The Begg-Mazumdar (Kendall's tau  $b=0.151$ ,  $p=0.09$ ) and Egger test (bias=0.98, 95% CI=-1.423.38,  $p=0.47$ ) indicated no publication bias. A visual inspection of the funnel plot revealed that there was some asymmetry in the plot, and we adjusted for this asymmetry and potential missing studies (see FigureS1 in the online data supplement). The trim-and-fill method demonstrated that the prevalence of remission was unaltered when adjusted for potential missing studies. Restricting the analysis to studies which used the RSWG criteria for remission (N=25 studies, N=6,909 patients), the overall pooled prevalence remission rate was 56.9% (95% CI=48.9-64.5, Q=656.9, N=25 studies). Using the worst case scenario, the remission rate was 39.3% (95% CI=35.1-43.5, Q=1371, N=55 studies).

#### ***Subgroup analyses of remission rates***

Full details of the proportion of people who experienced remission, together with

heterogeneity and trim and fill analyses are summarized in **Table 1**. Results of interest are briefly discussed below.

***Insert table 1 here***

For those studies with FES patients only, the pooled remission rate was 56.0% (95% CI=47.5-64.1, Q=378.50, N=25 studies), with an equivalent rate of 55.4% (95% CI=47.7-62.8, Q=1049.0, N=29 studies) for FEP patients; the pooled remission rate was higher in FE affective psychosis only patients (78.7%, 95% CI=63.9-88.5, Q=68.6, N=6 studies) compared to people with FES.

There were no differences in remission rates by the study period, duration of study follow up, study type or setting, or proportion of studies using narrow remission criteria. Remission rates were significantly higher in studies from Africa (73.1%, 95% CI=47.2-89.1, Q=2.48, N=2 studies), Asia (66.4%, 95% CI=55.8-75.5, Q=139.2, N=2 studies) and North America (65.2%, 95% CI=56.6-72.9, Q=192.7, N=17 studies) compared to other regions (including Europe and Australia).

### ***Meta regression of factors influencing remission rates***

Full details of the moderators of remission are presented in **Table 2**. Higher remission rates were associated with studies conducted in more recent years ( $\beta=0.04$ , 95% CI=0.01-0.08,  $p=0.018$ ,  $R^2=0.10$ ).

***Insert table 2 here***

### ***Rate of recovery***

Full details of the proportion of people who are recovered, together with heterogeneity and trim and fill analyses are summarized in **Table 3**.

***Insert table 3 here***

The pooled rate of recovery among 9,642 individuals with FEP was 37.9% (95% CI=30.0-46.5,  $Q=1450.8$ ,  $N=35$  studies,  $p=0.006$ ) (see Figure S3 in the online data supplement). The Begg-Mazumdar (Kendall's tau  $b=-1.0$ ,  $p=0.37$ ) and Egger test (bias=2.32, 95% CI=-1.77 – 6.42,  $p=0.25$ ) indicating no publication bias. A visual inspection of the funnel plot revealed that the plot was largely symmetric (see Figure S4 in the online data supplement). The trim-and-fill method demonstrated that the prevalence of recovery was unaltered when adjusted for potential missing studies. Assuming the worst case scenario technique, the pooled prevalence of recovery was 23.3% (95% CI=18.4-29.2,  $Q=1270$ ,  $N=33$  studies).

### ***Subgroup analyses of recovery rates***

For those studies using the narrowest recovery criteria, the recovery rate was 25.2% (95% CI=16.87-35.93,  $Q=885.45$ ,  $N=16$  studies). Further, the pooled prevalence of recovery was significantly higher in North America (Canada and USA) (71.0 %, 95% CI=56.8-82.0,  $Q=150.1$ ,  $N=10$  studies,  $p<0.001$ ) than Europe (21.8%, 95% CI=14.6-31.2,  $Q=434.2$ ,  $N=14$  studies), Asia (35.1%, 95% CI=22.1-50.7,  $Q=184.5$ ,  $N=8$  studies) and Australia (28.1%, 95% CI=10.0-57.9,  $Q=1.45$ ,  $N=2$  studies). Following the trim and fill analysis the recovery rate from North America decreased slightly to 68.5% (95% CI=48.6-83.4); there was a slight increase in the recovery rate seen in studies from Europe to 26.3% (95% CI=16.6-38.9). There were no significant difference in North American studies compared to studies from other regions in relation to attrition rate, average length of follow up (mean duration of follow up: North America 4.7 (SD=4.1) years vs other regions 7.8 (SD=5.8) years ( $t=-1.46$ ,  $p=0.15$ ), or the use of more narrow recovery criteria (although no studies North America used a recovery criterion of >2 years duration, compared to 8 studies from other regions which used this criterion ( $\chi^2=2.77$ ,  $p=0.052$ )). Additionally, those

studies with the longest follow up periods (>6 years) (32.4%, 95% CI=23.4-43.0, Q=250.5, N=15 studies) and with a 2-6 year follow up (32.30%, 95% CI=21.5-45.3, Q=462.0, N=11 studies) had significantly lower recovery rates than those studies with a 1-2 year follow up (54.1%, 95% CI=39.0-68.4, Q=167.0, N=9 studies) (p=0.044).

Equivalent rates of recovery were found in those with FEP (34.4%) and FES (30.3%) diagnoses. Those with a diagnosis of FE affective psychosis had a significantly increased pooled recovery rate (84.6%, 95% CI=64.0-94.4, Q=109.3, N=4 studies) compared to those with FEP (34.4% (95% CI: 25.2-44.9, Q=527.0, N=19 studies), and FES (30.3% (95% CI=19.7-43.6., Q=514.7, N=12 studies) (p=0.0031).

### ***Meta regression of factors influencing recovery rates***

Full details of the moderators of recovery are presented in **supplementary table 3**. Briefly, the meta regression analyses showed that higher rates of recovery were moderated by White ethnicity ( $\beta=0.02$ , 95% CI=0.01-0.04,  $p=0.002$ ,  $R^2=0.41$ ); whereas, lower rates of recovery were moderated by Asian ethnicity ( $\beta=-0.02$ , 95%CI=-0.04-0.00,  $p=0.019$ ,  $R^2=0.32$ ) and a higher loss to attrition (or drop-out rates) ( $\beta=-0.04$ , 95%CI=-0.07- -0.01,  $p=0.009$ ,  $R^2=0.21$ ).

### **Discussion**

This novel, large scale meta-analysis found that fifty-eight percent of FEP patients meet criteria for remission and 38% meet criteria for recovery over a mean of 5.5 and 7.2 years follow up respectively. Thirty percent of those with FES met the criteria for recovery. Our findings are particularly relevant given the previously reported lower rates of recovery in multi episode schizophrenia of 13%<sup>9</sup>. The average duration of follow up of 5.5 years in our remission sample and 7.2 years in our recovery cohort



adds further weight to the significance of our findings.

## **Remission**

Our findings for remission were remarkably stable and did not differ dependent on the use of more stringent criteria such as the RSWG (57%) or the use of broader criteria (59%). Our remission rate of 57% based on studies using the RSWG criteria, is higher than the rate of 40% identified in a systematic review from 2012.<sup>6</sup> Our study improves on this previous review by the inclusion of 25 studies using the RSWG criteria to define remission, as compared to 12 studies, and by having a longer average duration of follow up.

Few variables were found to be moderators of remission rates, and no patient level clinical or demographic variables were associated with remission. We identified that a more recent study period was associated with improved remission rates, perhaps reflecting the improved outcomes from FEP patients treated in dedicated early intervention services over the past two decades.

## **Recovery**

Our identified rate of recovery of 38% in FEP is higher than previously identified rates of 13.5% and 11-33% in multi episode schizophrenia.<sup>5,9</sup> Our imputed recovery rate of 23% based on the worst case scenario technique is equivalent to the recovery rate for those studies which defined recovery based on symptomatic and functional improvement sustained for more than 2 years. Further, this worst case scenario recovery rate of 23% remains higher than that identified in most recent review of multi episode schizophrenia outcomes by Jääskeläinen et al. Our pooled recovery rate is similar to the 42% who showed functional recovery in the systematic review of outcome in FEP by Menezes et al., though this 'good' outcome was based on data from 11 studies only,<sup>7</sup> whereas we included 39 studies with recovery as an outcome.

Further, in the review of Menezes et al, the 'good' outcome measure was based on an average follow period of 3 years, much shorter than our 7 year follow up. In our review, we report on studies with standardized definitions of recovery and comparisons between those with strict and broad definitions of recovery- in contrast to the Menezes et al, review, in which studies reporting on a wide variety of outcome measures (including some with definitions of remission and recovery) were combined into good, intermediate, and poor outcomes.<sup>7</sup>

One interesting finding is the significantly increased pooled prevalence of recovery identified in North America (Canada and USA) compared to all other regions. This regional variation in recovery was not accounted for by statistically significant differences in baseline clinical and demographic variables, or dropout rates. We identified that none of the North American studies used the more conservative two-year criterion to define recovery, compared to 32% (N=8) of studies from other regions, and only 11% (N=1) of North American studies had a follow up of longer than 6 years, compared to 52% (N=13) from other regions, differences which trended towards significance, and which potentially impacted on the improved recovery rate from this region. This finding warrants further investigation. It may be related to differences in the types of patients with FEP who were enrolled in North America compared to other regions. There may be other service level confounds which we were unable to investigate, such as an increased proportion of studies in North America occurring in academic centres, in which the potential for more intensive and multimodal treatment approaches may have been available. However, we were unable to assess the effects of variable treatments by region which may have contributed to improved recovery rates in North America. Further, the influence of potential non-representative sampling in North America<sup>97</sup> could not be accounted for.

We demonstrated for the first time in a large scale meta-analysis that recovery in FEP is not reduced with a longer duration of follow up. This finding, contrary to one of our hypotheses, was interesting, in that those with a follow up period greater than 6 years (32% recovery rate) and those with a 2-6 year follow up (32% recovery rate), had equivalent rates of recovery, indicating that the rate of recovery seen from 2-6 years, can be maintained for patients followed up beyond 6 years. This is in contrast to previous reviews that found an association between longer follow up duration and reductions in 'good' outcomes.<sup>7, 8</sup> If psychotic disorders, and more specifically schizophrenia are progressive disorders, then we might expect to see decreased recovery rates with longer periods of follow up. The fact that we have not identified any changes in recovery rates after the first two years of follow up indicates an absence of progressive deterioration. This suggests that patients with worse outcomes are apparent in the earlier stages of illness, rather than that the course of illness been a progressive one for the majority of patients.<sup>98</sup> This is supported by recent evidence indicating that treatment resistance in schizophrenia is present from illness onset for the majority who develop a treatment resistant course of illness.<sup>99</sup>

We hypothesised that a greater proportion of cases of FEP would have recovered in recent years. However, similar to earlier reviews in multi episode patients (and in contrast to our findings in relation to remission rates), we did not identify that recovery rates were increasing over time.<sup>5, 8, 9</sup> In fact, we identified a significantly reduced pooled recovery rate for studies conducted from 1997-2016 (32%) compared to the pooled recovery rate of 45% for studies conducted from 1976-1996. This finding in a FEP population indicates that thus far the dedicated and intensive specialist care provided for FEP patients over the past two decades has not resulted in improved recovery rates, even though remission rates were improved over the past two decades.

Knowledge of factors associated with increased recovery in FEP can help identify individuals in need of more robust interventions. However, we found few moderators of recovery in our meta-analysis. White ethnicity was associated with increased recovery, whereas Asian ethnicity was associated with lower recovery rates. Higher dropout rates moderated lower recovery, potentially indicative of a selection bias, in that those who are well, and are no longer in contact with mental health services may be disproportionately lost to follow up, thus impacting on the recovery rate.

### ***Duration of Untreated Psychosis***

A longer DUP was not a moderator of remission or recovery rates. This was a secondary outcome measure in our study, but despite that our findings are contrary to previous meta-analyses, which found that a shorter duration of untreated psychosis is associated with better outcomes.<sup>100</sup>

### **Strengths and Limitations**

While this is the first meta-analysis of remission and recovery in FEP, including a large data set of 19,897 FEP patients, we acknowledge some limitations.

First, there was considerable methodological heterogeneity across studies. Consequently, we encountered high levels of statistical heterogeneity, which is to be expected when meta-analysing observational data.<sup>15</sup> We followed best practice in conducting subgroup and meta regression analyses to explore potential sources of heterogeneity. However, the main results do not appear to be influenced by publication bias, and were largely unaltered after applying the trim-and-fill method. Further, for remission there was little variability in the overall rates of remission by definition of remission, study type and method of assessment used. Though the different definitions of recovery can provide an inflated rate of recovery, we provided data relating to studies with the most stringent criteria for recovery with symptomatic and functional recovery for more than 2 years (with an identified recovery rate of

22%). We further provided a worst case scenario rate for remission and recovery, imputing these values based on the trial number of recruited patients, and assuming that all those lost to follow up would not have met criteria for remission or recovery. Our findings therefore, offer valid measures of remission and recovery in FEP.

Second there was inadequate data on important confounders such as treatments given over the course of follow up, adherence with treatment, social functioning and symptom profile over the course of follow up, and lifestyle factors such as alcohol and substance use, precluding the meta analytic assessment of these factors as moderating or mediating variables. Future studies may wish to consider including data from intervention studies in FEP, to assess the influence of specific treatments, and adherence to treatment on remission and recovery rates in FEP.<sup>101</sup>

Third, data for this meta-analysis was extracted from baseline and follow up points from the individual studies, with limited information available in individual studies for the period during the follow up.

Fourth, while remission and recovery rates are provided at study endpoint, no data is available on those who met, and sustained criteria for remission or recovery for the entire duration of follow up, nor at what time point individuals met criteria for remission or recovery. The absence of such data does not allow for a more detailed description of illness trajectory. However, we have been able to delineate the effects of duration of study follow up on remission and recovery.

Fifth, while we identified studies from six regions of the world, there was marked variability in the number of studies from each region, with the majority of studies conducted in North America and Europe. In relation to the higher rate of recovery identified in North America compared to other regions, we cannot rule out confounding variables relating to differences in the types of patients with FEP who were enrolled in North America compared to other regions, and other service level

confounds which may have existed between regions. However, our finding of lower remission rates in Europe is consistent with findings from the prospective W-SOHO study on the outcome for multi-episode schizophrenia in an out-patient setting.<sup>102</sup>

Finally, consideration for the introduction of sampling bias due to the variability at the point of recruitment to FEP studies is required. Some may recover quickly from a FEP and not wish to participate, others may be severely unwell and unable to consent to participate, while community based FEP studies may be unable to recruit patients with more chaotic presentations.

## **Conclusions**

This is the first meta-analysis of remission and recovery rates, and moderators of these outcomes, in people with FEP, and the first meta-analysis pooling and comparing all available data across patients with FEP, FES and first episode affective psychosis. We provide evidence of higher than expected rates for remission and recovery in FEP. We confirm that recovery rates stabilise after the first two years of illness, suggesting that psychosis is not a progressive deteriorating illness state. While remission rates have improved over time, rates of recovery have not done so, potentially indicating that specialised FEP services in their current incarnation, while improving remission rates, have not provided improved longer term recovery rates.

Our study highlights a better long term prognosis in FEP and FES, and a more positive outlook for people diagnosed with FEP and FES, than has been suggested by previous studies, which included patients with multi episode schizophrenia.

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